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Short Communication

Hydroxylation of a Vitamin D A-Ring Fragment [1]

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Summary. When the benzoate of (*S*)-(*Z*)-2-(5-(*tert*-butyldimethylsiloxy)-2-methylencyclohexyliden)-ethanol (**5**) is treated with 2.5 equivalents of $Hg(OOCCF_3)_2$ in dry *THF*, a smooth and selective allylic hydroxylation occurs. The C-1 functionalized vitamin D A-ring synthon **6** is isolated in 65 to 70% yield in a single step.

Keywords. Vitamin D; Vitamin D A-ring fragment; C-1 Hydroxylation; $Hg(OOCCF_3)_2$.

Hydroxylierung eines Vitamin D A-Ring-Fragments (Kurze Mitt.)

Zusammenfassung. Umsetzung des Benzoats von (*S*)-(*Z*)-2-(5-(*tert*-Butyldimethylsiloxy)-2-methylencyclohexyliden)-ethanol (**5**) mit 2.5 Äquivalenten $Hg(OOCCF_3)_2$ in trockenem *THF* führt zu einer selektiven allylischen Hydroxylierung. Damit ist das an C-1 funktionalisierte Vitamin D A-Ring-Fragment **6** in einem einzigen Schritt in einer Ausbeute von 65 bis 70% zugänglich.

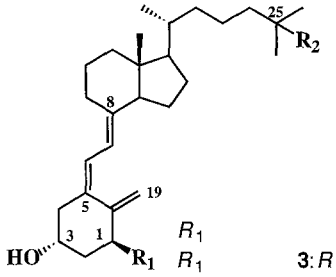
Introduction

Calcitriol (**1**, 1α,25-dihydroxyvitamin D_3) is the hormonally active form of vitamin D (**2**) which plays a central role in the calcium homeostasis [2]. Its classical biological responses are stimulating the intestinal calcium absorption (ICA) and bone calcium mobilization (BCM) [3]. Recently it has been shown that this hormone suppresses proliferation and induces differentiation in normal and malignant cells [4]. A serious drawback in the use of calcitriol in the treatment of certain cancers and skin disorders is its potent calcemic effect [5]. Therefore, many efforts have been directed towards the synthesis of various analogs of **1** having a more specific biological profile with the aim for therapeutic use [6]. One method for synthesizing side chain and/or CD-ring modified analogs has been pioneered by *Lythgoe* [7] using *Wittig-Horner* or *Julia* methodologies for the coupling of the A-ring fragment with the upper part of the molecule. This approach has now become one of the standard methods in the construction of the triene moiety of vitamin D [8]. A shortcome of this route is the synthesis of the chiral A-ring fragment **3** which requires up to 15 steps. A much shorter and simpler access to this valuable synthon is therefore demandable. In this Short Communication we disclose a new direct

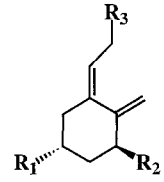
method for the introduction of the biologically important 1α-hydroxyl function into the A-ring fragment of vitamin D.

Results and Discussion

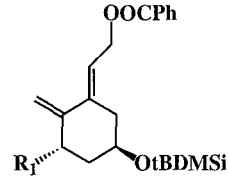
In our continuous search for selective transformations of the vitamin D triene moiety we turned our attention towards reacting vitamin D with various mercury salts. Mercury salts are well known to achieve allylic oxidations [9], although not too many examples are reported in the steroidal field due to the poor reactivity and forced reaction conditions of such reagents [10]. Recently we disclosed our findings of the selective transformation of vitamin D into a C-19 functionalized isovitamin D derivative which can be utilized for introducing the C-1 hydroxyl group into the vitamin D skeleton [11]. We now want to report our results upon the application of this reaction to the A-ring fragment of vitamin D.



1: $R_1 = R_2 = OH$
2: $R_1 = R_2 = H$



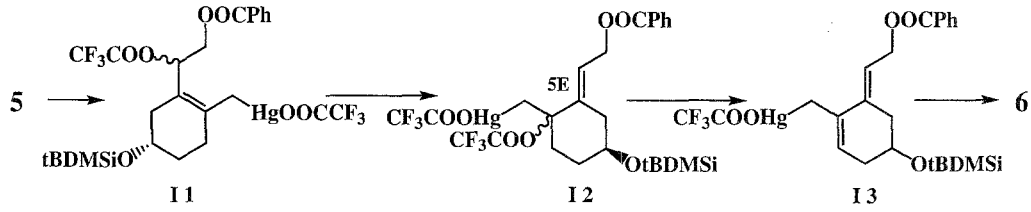
3: $R_1 = R_2 = O^tBDMSi$, $R_3 = POPh_2$
4: $R_1 = O^tBDMSi$, $R_2 = H$, $R_3 = OH$
5: $R_1 = O^tBDMSi$, $R_2 = H$, $R_3 = OOCPh$



6: $R_1 = OOCCF_3$
7: $R_1 = OH$

(*S*)-(*Z*)-2-(5-(*tert*-Butyldimethylsiloxy)-2-methylencyclohexyliden)-ethanol (**4**; in the following, this compound will be called "A-ring fragment", and the steroid numbering scheme will be used) is readily available by a three step degradation sequence ($KMnO_4$ oxidation, silylation, and $Pb(OAc)_4$ cleavage/reductive work-up) [12] of vitamin D. When **5** is treated with 2.5 equivalents of $Hg(OOCCF_3)_2$ in dry *THF* at room temperature, a smooth and selective allylic oxidation occurs. After reductive work-up, compound **6** is routinely isolated in yields of 65 to 70%. The allylic oxidation is stereospecific and creates the natural configuration at C-1. During the reaction, a 5*Z* to 5*E* double bond isomerization takes place. To proof the structure and the stereochemistry of **6**, this compound was independently synthesized *via* the following sequence: 5*Z* to 5*E* isomerization in **5** was accomplished by SO_2 addition and subsequent cycloreversion [13]; the introduction of the 1α-trifluoroacetate group was performed by SeO_2 oxidation [14], followed by esterification with $(CF_3CO)_2O$/pyridine.

Following this reaction by ^1H NMR spectroscopy (*THF*-d_8, RT) showed that an almost complete conversion from **5** to **6** occurs. A ^1H NMR study at lower temperature (0°C) revealed additional sets of signals indicating that this reaction proceeds *via* consecutive intermediates. From our preliminary NMR data we propose the mechanism given in Scheme 1 for this allylic oxidation. In the first step, mercury trifluoroacetate adds across the diene to give intermediate **I1**. Subsequent sigmatropic rearrangement and elimination of CF_3COOH yields **I3** *via*



Scheme 1

I2. At this stage, the 5*Z* to 5*E* isomerization takes place. We assume that the final introduction of the allylic trifluoroacetate proceeds by a SN′-type displacement of the $HgOOCCF_3$ moiety in **I3**. Results of a more detailed mechanistic study of this reaction will be published elsewhere in due course.

Experimental

(3S)-(75R-(E)-2-(3-(Trifluoroacetoxy)-5-(tert-butyldimethylsiloxy)-2-methylene-cyclohexylidene)-1-benzoyloxy-ethane (**6**)

To a stirred solution of 0.100 g (0.27 mmol) of **5** in 1.5 ml dry *THF*, a solution of 0.256 g (0.6 mmol) $Hg(OOCCF_3)_2$ in 1 ml dry *THF* was added dropwise, and the resulting mixture was stirred at RT for 24 h. After cooling to 0°C, a small amount of $NaBH_4$ and a few drops of MeOH were added. The precipitate was filtered off and the filtrate was concentrated. Flash chromatography (silica gel; hexanes:ethylacetate = 9:1) gave 0.078 g (0.17 mmol; 65%) of **6**.

$R_f = 0.65$; ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 8.03$ (m, 2H, 2H-aromat), 7.55 (m, 1H, 1H-aromat), 7.42 (m, 2H, 2H-aromat), 5.89 (tt, $J = 6.75$ Hz, 1.25 Hz, 1H, 6-H) 5.74 (dd, $J = 7.0$ Hz, 4.5 Hz, 1H, 1β-H), 5.25 (t, $J = 1$ Hz, 1H, 19-H), 5.06 (t, $J = 1.25$ Hz, 1H, 19-H′), 4.93 (dd, $J = 13$ Hz, 7 Hz, 1H, 7-H), 4.83 (dd, $J = 13$ Hz, 7 Hz, 1H, 7-H′), 4.19 (septet, $\nu_{1/2} = 15$ Hz, 1H, 3α-H), 2.61 (dd, $J = 13.75$ Hz, 3.5 Hz, 1H, 4α-H), 2.36 (dd, $J = 13.75$ Hz, 7.5 Hz, 1H, 4β-H), 2.24 (m, 2H, 2-H_2), 0.86 (s, 9H, *t*-BuSi), 0.09 (s, 6H, Me_2Si) ppm.

(3S)-(5R)-(E)-2-(3-(Trifluoroacetoxy)-5-(tert-butyldimethylsiloxy)-2-methylene-cyclohexylidene)-1-benzoyloxy-ethane (**7**)

To a solution of 0.078 g (0.17 mmol) **6** in 3 ml MeOH, three drops of a methanolic NaOH solution ($pH = 9$) were added. After 1 h at RT (TLC control) the reaction mixture was quenched with aqueous HCl (5%) and extracted with ether. The organic phase was washed with brine, dried over $MgSO_4$, and concentrated. Flash chromatography (silica gel; hexanes:ethylacetate = 1:1) afforded 0.052 g (78%) of **7**.

$R_f = 0.21$; ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 8.04$ (m, 2H, 2H-aromat), 7.75 (m, 1H, 1H-aromat), 7.41 (m, 2H, 2H-aromat), 7.85 (tt, $J = 7.15$ Hz, 1.3 Hz, 1H, 6-H), 5.09 (t, $J = 1.35$ Hz, 1H, 1H, 19-H), 4.99 (t, $J = 1.65$ Hz, 1H, 19-H′), 4.92 (dd, $J = 12.93$ Hz, 7.15 Hz, 1H, 7-H), 4.82 (dd, $J = 12.93$ Hz, 7.15 Hz, 1H, 7-H′), 4.51 (dd, $J = 7.2$ Hz, 4.4 Hz, 1H, 1β-H), 4.24 (septett, $\nu_{1/2} = 13.5$ Hz, 1H, 3α-H), 2.51 (dd, $J = 14.0$ Hz, 3.65 Hz, 1H 4α-H), 2.37 (dd, $J = 14.0$ Hz, 6.60 Hz, 1H, 4β-H), 1.90 (m, 2H, 2-H_2), 0.89 (s, 9H, *t*-BuSi), 0.05 (s, 6H, Me_2Si) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 166.5$ (C=O), 151.7 (C-10), 141.1 (C-5), 132.9 (C-aromat), 130.3 (C-aromat), 129.6 (C-aromat), 128.3 (C-aromat), 121.0 (C-6), 109.2 (C-19), 70.3 (C-1), 66.5 (C-3), 61.2 (C-7), 42.8 (C-8), 37.4 (C-4), 25.7 ($SiC(CH_3)_3$), 18.0 ($SiC(CH_3)_3$), −4.8 ($Si(CH_3)_2$) ppm; IR (neat): $\nu = 3670$, 2955, 2926, 2855, 1720,

1602, 1452, 1315, 1270, 1098, 1070, 1025, 836, 712, 606 cm^{-1}; FI-MS (120°C, 8 kV, 3 mA): $m/z = 388\ (M^+)$.

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